CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212209Orig1s000

CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF HEMATOLOGIC MALIGNANCIES 2

MEMORANDUM

DATE: 09AUG2022

FROM: Candis Morrison, PhD, CRNP - Clinical Analyst

SUBJECT: NDA 212209 Bendamustine Class 1 Resubmission

TO: Electronic Document Record

THROUGH: Nicholas Richardson, DO, MPH - Clinical Team Lead

There are no changes in this resubmission that would alter the Division's conclusion that this NDA can receive tentative approval for the specified indications. For specific details regarding the submission, please see initial clinical review dated 25FEB2022.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CANDIS MORRISON
08/10/2022 01:34:07 PM

Memorandum
Clinical Review 505(b)(2) NDA
Division of Hematologic Malignancies 2

Date	25 February 2022
NDA/BLA #	NDA 212209
Applicant	Slayback Pharma LLC
Date of Submission	16 June 2021
PDUFA Goal Date	16 March 2022
Drug	Bendamustine Hydrochloride
Dosage form(s) / Strength(s)	100mg/4mL (25 mg/mL)
Clinical Reviewer	Candis Morrison, PhD, CRNP
Clinical Team Lead	Nicholas Richardson, DO MPH
Signatory	Nicole J. Gormley, MD
Applicant Proposed Indication(s)/Population(s)	• Treatment of patients with chronic lymphocytic leukemia • Treatment of patients with indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen
Recommendation on Regulatory Action	Tentative Approval
Recommended Indication(s)/Population(s) (if applicable)	• Treatment of patients with chronic lymphocytic leukemia • Treatment of patients with indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen

Summary

Regulatory History

- 31 August 2018: New drug application (NDA) submitted for Bendamustine Hydrochloride Injection, 100 mg/4 mL (25 mg/mL) via a 505(b)(2) pathway. The indications sought for licensure were the same as the listed drug Bendeka (NDA 208194).

- 17 June 2019: Complete response letter issued. Manufacturing facility issues.
- 01 July 2019: Class 2 resubmission
- 16 September 2019: Complete response letter issued. Manufacturing facility issues.
- 14 February 2020: Class 2 resubmission
- 02 July 2020: Granted tentative approval
- 16 June 2021: Class 2 resubmission

This Class 2 resubmission is to support proposed changes to the tentatively approved product as shown in the table below. The listed drug for this application is Belrapzo (NDA 205580)

	Existing Tentatively Approved NDA	Proposed Changes to Tentatively Approved NDA	Justification
Diluent	0.9% Sodium Chloride Injection USP	0.9% Sodium Chloride Injection USP and/or 2.5% Dextrose/0.45% Sodium Chloride Injection USP	To propose new diluent in line with the RLD (BELRAPZO™).
Recommended Diluent Volume (Infusion Bag Volume)	(b) (4) mL	250 mL	(b) (4)
Infusion Rate	**CLL:** (b) (4) Minutes **NHL:** Minutes	**CLL:** 20 Minutes **NHL:** 20 Minutes	
Final Diluted Drug Product Concentration	(b) (4) mg/mL to (b) (4) mg/mL	(b) (4) mg/mL to 1.36 mg/mL	

No clinical data was included in the submission. The proposed indications are the same as those for the listed drug, Belrapzo.

For Dosage and Administration, the Applicant originally provided data to support a lower concentration range of (b) (4) mg/mL (see table above). This supported a minimum volume of (b) (4) mL to be administered and be within the final concentration range supported by the data. Any volume less than (b) (4) mL was outside the range for which the data supported. With the lower concentration range of (b) (4) mg/mL, some dose modifications for (b) (4) mg/m^2, (b) (4) mg/m^2, (b) (4) mg/m^2, and (b) (4) mg/m^2 were not feasible. To address this, the Applicant submitted updated data to support a lower concentration range of 0.1 mg/mL, which would allow for all possible dose modifications. The additional data to support the lower concentration range was deemed acceptable by the CMC review team (see CMC for additional information). Given the updated concentration range of 0.1 mg/mL to 1.36 mg/mL, Section 2 of the label was consistent with the listed drug Belrapzo.

The Applicant also updated the label to incorporate the Warning and Precaution for Progressive Multifocal Leukoencephalopathy and updated the Warning and Precaution for Other Malignancies to include information on non-melanoma skin cancer.

Conclusion: There is no clinical data submitted with this 505(b)2 NDA submission for

bendamustine hydrochloride. Based on the clinical review, NDA 212209 for bendamustine for the 1) *treatment of patients with chronic lymphocytic leukemia* and 2) *treatment of patients with indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen* can be granted tentative approval.

See the Labeling and CDTL Review for additional information for this application.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICHOLAS C RICHARDSON on behalf of CANDIS MORRISON
02/26/2022 08:03:10 AM

NICHOLAS C RICHARDSON
02/26/2022 08:03:37 AM

NICOLE J GORMLEY
02/26/2022 01:07:16 PM

Clinical Review

Date	22JUN2020
From	Candis Morrison, PhD, CRNP
Subject	Clinical Review
NDA/BLA # Supplement#	NDA 212209 (Class 2 Resubmission)
Applicant	Slayback Pharma, LLC
Date of Submission	14FEB2020
PDUFA Goal Date	14AUG2020
Proprietary Name / Non-Proprietary Name	Bendamustine Hydrochloride Injection
Dosage form(s) / Strength(s)	Injection: 100 mg/4 mL (25mg/mL) of bendamustine hydrochloride in a multiple-dose vial
Applicant Proposed Indication(s)/Population(s)	• Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established. • Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Recommendation on Regulatory Action	Tentative Approval
Recommended Indication(s)/Population(s) (if applicable)	Not applicable

Summary

There are no clinical data submitted with this 505(b)(2) application. The Application will receive a *Tentative Approval*.

The clinical sections of the label were reviewed, and the final agreed upon labeling was submitted on 08JUN2020Refer also to labeling review completed by Stacy Shord, Pharm D, 08JUN2020.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CANDIS MORRISON
06/23/2020 06:40:34 AM

NICHOLAS C RICHARDSON
06/26/2020 07:08:23 AM

Clinical Review

Date	20 May 2019
From	R. Angelo de Claro, MD
Subject	Clinical Review
NDA/BLA # Supplement#	NDA 212209
Applicant	Slayback Pharma, LLC
Date of Submission	31 August 2018
PDUFA Goal Date	30 June 2019
Proprietary Name / Non-Proprietary Name	Bendamustine Hydrochloride Injection
Dosage form(s) / Strength(s)	Injection: 100 mg/4 mL (25mg/mL) of bendamustine hydrochloride in a multiple-dose vial
Applicant Proposed Indication(s)/Population(s)	• Chronic lymphocytic leukemia (CLL). Efficacy relative to first line therapies other than chlorambucil has not been established. • Indolent B-cell non-Hodgkin lymphoma (NHL) that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.
Recommendation on Regulatory Action	*Complete Response*
Recommended Indication(s)/Population(s) (if applicable)	Not applicable

Summary

There are no clinical data submitted with this 505(b)(2) application. Application will receive a complete response due to CMC issues. Labeling and 505(b)(2) assessment review will be completed with application resubmission.

Refer also to labeling review completed by Virginia Kwitkowski, MS, ACNP-BC on January 31, 2019.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROMEO A DE CLARO
05/20/2019 11:18:34 AM